

# Risk Factors for the Occurrence of Erosive Esophagitis in Patients with Dyspepsia

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## ABSTRACT

**Background:** The prevalence of erosive esophagitis tends to increase recently. It induces higher medical expense, loss of working time, and decreases quality of life. However the study on risk factors of erosive esophagitis scarcely reported in Indonesia. This study aimed to find the association between age, sex, smoking, alcohol drinking, body mass index, hiatal hernia, the use of non steroidal anti-inflammatory drugs (NSAID), and drugs that decrease lower esophageal sphincter (LES) tone with the occurrence of erosive esophagitis in dyspeptic patients.

**Method:** A case-control study was conducted on patients with dyspepsia who underwent upper gastrointestinal endoscopy procedure and had been interviewed to determine risk factors for erosive esophagitis in July - September 2008. The association between risk factors and the occurrence of erosive esophagitis were analyzed using Chi-square, which subsequently revealed  $p < 0.25$ , this variable included in multivariate analysis.

**Results:** There were 135 patients fulfilled criteria; 45 cases and 90 controls. The association was found between the occurrence of erosive esophagitis in dyspeptic patients and smoking more than 15 cigarette/day (OR 15.43;  $p = 0.00$ ; CI 95% 4.77-49.88), the use of NSAID (OR 9.49;  $p = 0.00$ ; CI 95% 2.77-32.53) and the consumption of drugs that decrease LES tone (OR 3.56;  $p = 0.02$ ; CI 95% 1.26-10.02).

**Conclusion:** Smoking more than 15 cigarettes/day, use of NSAID and drugs that decrease LES tone is a risk factors for the occurrence of erosive esophagitis.

**Keywords:** erosive esophagitis, NSAID, smoking, drugs that decrease LES tone

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a pathologic condition of the esophagus which is caused by the reflux of gastric contents into the esophagus, causing the symptoms and complications.<sup>1-4</sup> GERD, erosive esophagitis in this case, in this case, a role in increased cost for diagnostic and long-term treatment, the decrease of quality of life, and time to work. The greatest fear is the occurrence of the complications of GERD, which is esophageal stricture, Barrett's esophagus, and adenocarcinoma.<sup>3-5</sup>

The incidence of GERD is quite high. Prevalence in the Western countries 10-20%, but only 3-5% in Asia, except in Japan 13-15% and Taiwan + 15%.<sup>5</sup> Syam et al reported an increase of esophagitis prevalence of 5.7% in 1997 to 25.18% in 2002 (mean 13.13%) in 1,718 patients who underwent upper gastrointestinal endoscopy procedure with an indication of dyspepsia during the five years (1997-2002).<sup>2</sup>

A multicenter study in Germany conducted on 6,215 patients, concluded that male, alcohol consumption, history of GERD more than a year, and a smoker, significantly cause erosive esophagitis.<sup>6</sup> A casecontrol study in Illinois reported that hiatal hernia is a strong risk factor for the occurrence of erosive esophagitis. The use of nonsteroidal antiinflammatory drugs (NSAID) increase the risk for

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esophageal ulcer.<sup>7</sup> Another study in China reported age > 65 years old and tea drinker as risk factors for erosive esophagitis.<sup>8</sup> A multicenter study conducted in Korea reported risk factor for erosive esophagitis is a body mass index (BMI) > 25 kg/m<sup>2</sup>. Other studies on Korean population demonstrated that abdominal obesity is an even bigger risk factor for erosive esophagitis compared with BMI.<sup>9,10</sup> In Indonesia, there are no data on risk factors for the occurrence of erosive esophagitis. Thus, a study on factors contributing to the occurrence of erosive esophagitis that are considered by the clinician to the basic prevention and treatment of erosive esophagitis.

## METHOD

This study uses a case-control design to obtain association between the risk factors and the occurrence of erosive esophagitis in patients with dyspepsia who underwent upper gastrointestinal endoscopy procedure. The study conducted from July to September of 2008. Samples are obtained from provided population who fulfilled the criteria for study subjects, recruited by consecutive sampling method.

The inclusion criteria for the case group were patients aged > 18 years who underwent gastrointestinal endoscopy procedure with dyspepsia as indication and had been diagnosed with erosive esophagitis. Meanwhile, the control group used for patients without erosive esophagitis. The exclusion criteria are the finding of esophageal malignancy, stricture, infection, history of digesting corrosive substances, pyloric stenosis, achalasia, post gastrectomy, patients who underwent endoscopic procedure (for ligation, polypectomy, sclerotherapy), those with a habit of herbal drinking for arthritis within the last 1 month, having scleroderma or pregnancy, and unwillingness to participate in the study. Estimated minimum sample size calculated with the number of samples was measured using the formula for estimating the number of samples for testing hypothesis for 2 proportions, using the comparison of the number of cases and control 1 : 2 was obtained as much as 45 cases and 90 control.

The measurement was conducted on the anamnesis of age, sex, smoking history, history of NSAIDs use, alcohol drinking, consumption of drugs that decrease lower esophageal sphincter (LES) tone, and examination of body weight and height. Bivariate analysis performed on each of the risk factors for the occurrence of erosive esophagitis by Chi-square test to obtain p value, odds ratio (OR), and 95% confidence interval (CI). Risk factors in bivariate analysis gives a value of  $p < 0.25$  will be included in the multivariate analysis of logistic regression

techniques to obtain adjusted OR for each risk factors most associated with the occurrence of erosive esophagitis. The significance limit used in this study was 5% with 95% confidence interval. Data management and analysis performed using SPSS 15.0 statistical computer program.

## RESULTS

During July to September 2008, 45 cases and 90 controls for the study fulfilling the subject criteria were obtained. The study subjects involved patients who had been the outpatients of internal medicine polyclinic and the endoscopy unit of Cipto Mangunkusumo hospital. The number of patients being obtained in accordance with the calculation of sample size. In this study, out of 135 dyspeptic patients which had undergone gastrointestinal endoscopy procedure, showed the following demographic characteristics such as shown in table 1. The method of data collection relied on the memory of the patients and thus were subjected to bias (recall bias) which is a weakness of this study.

In this study, the mean of age in cases group was older than the control group. The number of male patients was higher in the cases group than in the control group. In this study, the proportion of patients who smoke was higher in the cases group than the control group (37.8% vs 5.6%). The proportion of hiatus hernia is more in the case group than the control group, as well as body mass index BMI > 25 kg/m<sup>2</sup>, using alcohol, NSAIDs, and drugs that decrease LES tone.

Table 1. Patients characteristic

Characteristic	Cases n (%)	Control n (%)
Age (years)	46.4 ± 15.6	42.4 ± 13.2
BMI (kg/m <sup>2</sup> )	22.9 ± 4.2	22.3 ± 4.1
≥ 25	17 (37.8)	21 (23.3)
< 25	28 (62.2)	69 (76.7)
Sex (male)	25 (53.3)	41 (45.6)
Smoking (cigarette/day)		
≥ 15	17 (37.8)	5 (5.6)
< 15	28 (62.2)	85 (94.4)
Alcohol consumption	7 (15.6)	2 (2.2)
Drugs that decrease LES tone	12 (26.7)	13 (14.4)
NSAIDs consumption	12 (26.7)	5 (5.6)
Hiatal hernia	5 (11.1)	5 (5.6)
Chief complaints		
Epigastric pain	34 (75.6)	61 (67.8)
Abdominal bloating	2 (4.4)	7 (7.8)
Nausea	2 (4.4)	8 (8.9)
Chest pain	2 (4.4)	2 (2.2)
Difficulty swallowing	2 (4.4)	0
Others	3 (6.7)	12 (13.3)
Ethnic		
Batak	13 (28.9)	8 (8.9)
Javanese	9 (20.0)	31 (34.4)
Sundanese	5 (11.1)	19 (21.1)
Minangkabau	4 (8.9)	11 (12.2)
Betawi	2 (4.4)	9 (10.0)
Others	12 (26.7)	12 (13.3)
Esophageal endoscopy result		
Degree A	28 (62.2)	
Degree B	11 (24.4)	
Degree C	3 (6.7)	
Degree D	3 (6.7)	

In the cases group showed erosive esophagitis 62.2% of degree A, 24.4% of degree B, and 6.7% of degree C and D. The most dominant chief complaint in both groups was epigastric pain. In cases group, the most dominant tribe was Batak, while in the control group it was Javanese.

NSAIDs used by the patients include diclofenac, mafenamic acid, aspirin, ketoprofen, ketorolac, meloxicam and ibuprofen combined with aspirin. Meanwhile, the used drugs that decrease LES tone include progesterone, nifedipine, teophyllin, nitrate, and amlodipine.

To obtain the association between various risk factors and the occurrence of erosive esophagitis, analysis was performed using Chi-square test found that the factors which had significant relation were smoking more than 15 cigarettes/day ( $p = 0.00$ ), alcohol drinking ( $p = 0.00$ ) and the use of NSAIDs ( $p = 0.00$ ), as shown in table 2.

To determine the risk factors which were most associated with the occurrence of erosive esophagitis, risk factors in bivariate analysis gives a value of  $p < 0.25$  included in multivariate analysis model. With logistic regression technique showed that in fact the use of NSAIDs, drugs that decrease LES tone, and smoking more than 15 cigarettes/day showed statistical significance (table 3). In multivariate analysis, some variables showed statistically insignificant, such as age, sex, BMI  $> 25 \text{ kg/m}^2$ , hiatal hernia, and alcohol consumption.

## DISCUSSION

In this study, out of 135 dyspeptic patients (45 cases, 90 controls) who underwent gastrointestinal endoscopy procedure, the mean of age in cases group was older than the control group, the number of male patients was higher in the cases group than that in the control

group. The proportion of hiatal hernia was higher in the cases group compared to that in the control group (11.1% vs 5.6%). A study in Korea, a similar proportion resulted, which had been 11.7% and 14.3%.<sup>9,10</sup> The difference was shown in a study in America, where hiatal hernia could be found in about 70% patients with erosive esophagitis.<sup>7,11</sup> The proportion of patients who smoke was higher in the cases group than that in the control group (37.8% vs 5.6%). Similarly, the proportion of BMI  $> 25 \text{ kg/m}^2$ , alcohol drinking, NSAIDs, and drugs that decrease LES tone. These were not different from a study by Labenz et al.<sup>6</sup>

From endoscopy results of 45 cases of abnormalities erosive esophagitis, 62.2% degree of A, 24.4% degree B, and 6.7% degree C and D. This endoscopy results is rather different than study by Syafruddin et al who found mild esophagitis (grade I and II of Savary-Miller classification) as much as 90%, while severe esophagitis (grade III and IV) were not found.<sup>1</sup>

The most dominant chief complaint in both groups was epigastric pain. This result matched that of the study conducted by Poerniati, that the subjective symptom of GERD is severe epigastric pain.<sup>12</sup> Syam et al, reported that most patients with reflux esophagitis come with dyspeptic symptoms (75.11%) and only 9.71% with characteristic symptom of gastroesophageal reflux.<sup>2</sup> This is different than studies abroad, which often find chest pain and regurgitation as the dominant symptoms.<sup>12</sup>

The result of this study showed no difference in the risks for erosive esophagitis patients with age  $> 40$  years compared with patients  $< 40$  years. A cohort study conducted by Labenz et al with 6,215 samples showed that age was not associated with the occurrence of erosive esophagitis.<sup>6</sup> A similar

**Table 2. The association between various risk factors and the occurrence of erosive esophagitis**

Risk factor	Cases n (%)	Control n (%)	Crude OR (CI 95%)	p*
Male	25 (53.6)	41 (46.5)	1.49 (0.73-3.07)	0.27
Age $\geq 40$ years	31 (68.9)	51 (56.7)	1.69 (0.8-3.61)	0.17
Smoking $\geq 15$ cigarettes/day	17 (37.8)	5 (5.6)	10.32 (3.5-30.54)	0.00
Alcohol consumption	7 (15.6)	2 (2.2)	8.11 (1.61-40.83)	0.00
Drugs that decrease LES tone	12 (26.7)	13 (14.4)	2.15 (0.89-5.22)	0.09
NSAIDs consumption	12 (26.7)	5 (5.6)	6.18 (2.02-18.91)	0.00
Hiatal hernia	5 (11.1)	5 (5.6)	2.13 (0.58-7.76)	0.25
BMI $\geq 25 \text{ kg/m}^2$	17 (37.8)	21 (23.3)	1.99 (0.92-4.33)	0.08

p\* Chi-square test

**Table 3. The result of multivariate analysis for risk factors of the occurrence of erosive esophagitis**

Variables	OR (95% CI)	p
Smoking $\geq 15$ cigarettes/day	15.43 (4.77-49.88)	0.00
NSAIDs consumption	9.49 (2.77-32.53)	0.00
Drugs that decrease LES tone	3.56 (1.26-10.02)	0.02

result was obtained from a cross sectional study of 2,457 patients conducted by Kang et al.<sup>10</sup> However, a study by Juan et al using cross sectional design on 2,231 patients concluded that age of > 65 years associated with the occurrence of erosive esophagitis.<sup>8</sup>

On study in the United Kingdom, the incidence of GERD increases in concordance with age.<sup>13,14</sup> A study in Georgia Medicaid showed similar trend. This study reported increased risk with age.<sup>13,15</sup> Elderly associated with increased risk of erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma.<sup>8</sup> This is due to the co-morbidities found in elderly that require various kinds of medication, such as NSAIDs and anti-hypertension drugs which also risk factors for erosive esophagitis. Besides increasing age would also causes atrophy of gastric mucosal cells, reduction of esophageal clearance, and production of saliva.

The age limit used in this study were > 40 years due in accordance with The Indonesian Society of Gastroenterology Consensus.<sup>16</sup> In other Asian countries, the age limit of 35 years old is used.<sup>5</sup> Other studies using > 65 years age limit, so we get the association between the age > 65 years with the occurrence of erosive esophagitis.<sup>8</sup>

In previous studies indicated that male is a risk factor for erosive esophagitis. This is due to less parietal cell in female, so the risk of erosive esophagitis is lower.<sup>8</sup> In this study, there was no significant association to the occurrence of erosive esophagitis in males compared with females.

In a cross sectional and a longitudinal study that investigated the influence of sex in symptoms of GERD, no significant association was found.<sup>13</sup> Meanwhile, other studies found that male is a risk factor for erosive esophagitis.<sup>6,8-10</sup> Juan et al conducted a cross sectional study on 2,231 patients, and concluded that male is a risk factor for erosive esophagitis.<sup>8</sup> A study by Kim et al on 25,536 patients concluded that male proved significantly a risk factor.<sup>9</sup>

This study showed that significantly, the habit of smoking over 15 cigarettes/day is a risk factor for erosive esophagitis compared with patients who smoke less than 15 cigarettes/day or not smoking. A study by Juan et al on 2,231 patients supported this result, that heavy smoker (> 20 cigarettes/day) is a significant risk factor for erosive esophagitis.<sup>8</sup> Other studies showed no significant association between smoking and the occurrence of erosive esophagitis. Because in these studies, limits the consumption of cigarettes per day which is not classified as heavy smokers investigated.<sup>6,9,10</sup>

In this study defined the limit of smoking more than 15 cigarettes/day based on a study conducted by

Stanciu et al on 25 smokers more than 15 cigarettes/day who presented with the symptoms of GERD, in whom were found that decrease LES tone due to smoking, followed with acid reflux symptoms. This happened due to the blockade of cholinergic control mechanism by nicotine, so that relaxation of circular muscle cells of LES occurred. Kahrilas found that: (1) In the smokers, the tone of LES is significantly lower in comparison to non-smokers; (2) Period of smoking associated with an increased incidence of acid reflux frequency, which is induced by the mechanisms of deep breathing or coughing.<sup>17,18</sup>

In the habit of alcohol drinking, showed OR 8.11 (CI 95% 1.61 to 40.83) and  $p = 0.00$ , thus there is a possibility of significant association for the occurrence of erosive esophagitis. However, in multivariate analysis, this factor of alcohol consumption apparently showed no related to the occurrence of erosive esophagitis. This can explain the significance of these changes is the proportion of patients who are alcohol drinkers was a lot bigger than the proportion of non-alcohol drinkers who did not smoke (77.8% vs 22%). This showed that the factor of smoking of over 15 cigarettes/day really influence the factor of alcohol drinking in relation to the occurrence of erosive esophagitis.

Other studies conducted by Juan et al on 2,231 patients concluded that alcohol drinking is associated to the occurrence of erosive esophagitis. Other studies by Labenz et al also reported the same thing.<sup>6,8</sup> The difference in results probably due to differences in research methods and sample size. In a study conducted by Juan et al, the limit for alcohol consumption > 210 g/week, while in this study the limit used was a minimum of once a week.<sup>8</sup> In this study, the number of patients with alcohol-drinking habit is only a few, this is due to Islamic religious teaching which forbids alcohol, while the majority of patients' religion is Moslem.

The study by Kang et al on 2,457 patients concluded that the use of NSAIDs is a risk factor for erosive esophagitis, with OR 2.23 (CI 95% 1.14-4.35).<sup>10</sup> Meanwhile, in other studies by Avidan et al and Labenz et al did not support it.<sup>6,7</sup> This study showed that a significant association was found between the occurrence of erosive esophagitis with NSAIDs use compared with patients who did not use NSAIDs, as had been found in other studies.

A study by El-Serag demonstrated that there is a consistent increase of the risk for esophagitis and esophageal stricture in patients who received NSAIDs therapy.<sup>20</sup> Mechanism of NSAIDs in causing esophageal disorders is not fully understood, the following possibilities: (1) Direct toxicity on cells: in GERD, acidic pH in lower esophagus causes

the formation of fat-soluble NSAIDs which can penetrate the mucosal cells; (2) Destructive mucosal defense: eliminating the effect of NSAIDs inhibit the secretion of mucus and bicarbonate of esophageal mucosa; (3) Inhibition of prostaglandin synthesis: prostaglandin function against acid, bile salts or radiation. The effect on motility of the esophagus is still questionable, because a recent study failed to prove an effect in LES tone.<sup>15,19,20</sup>

This study showed no difference in the risk of erosive esophagitis in patients who have hiatal hernias and there were no hiatal hernia. In contrast, a case-control study by Avidan et al showed hiatal hernia as a risk factor for erosive esophagitis.<sup>7</sup> Similarly, cross-sectional study conducted Kim et al and Kang et al showed a significant relationship between the occurrence of erosive esophagitis with hiatal hernia.<sup>9,10</sup>

The association between hiatal hernia and GERD had been demonstrated in several studies, but not yet fully understood. Many theories had tried to explain the association between hiatal hernia and the occurrence of reflux. There is an opinion that hiatal hernia is the main etiology of GERD. Last theory is referred to as the 'sump theory', which states that when clearance from acid occurs, a small amount of gastric acid shall be trapped in the herniated part of the stomach above the diaphragm. Relaxation of lower esophageal sphincter during ingestion shall cause reflux.<sup>21-25</sup>

We have not been able to prove an association between occurrence hiatal hernia with erosive esophagitis, this was due to the fact that hiatal hernia cases were rarely found on patients (11.1% of cases vs 5.6% of control). The result is similar to the study by Kang et al, found that the proportion of hiatal hernia diagnosed in oriental ethnic is smaller than that in Caucasians (5% vs 24%).<sup>26</sup>

This study showed no difference in risk for the occurrence erosive esophagitis in patients with BMI > 25 kg/m<sup>2</sup> and < 25 kg/m<sup>2</sup>. A cross sectional study conducted by Kang et al in 2,457 patients, found that BMI > 25 kg/m<sup>2</sup> not associated with the occurrence of erosive esophagitis.<sup>7</sup> Meanwhile, studies by Kim et al and Labenz et al show results related to the occurrence of erosive esophagitis.<sup>6,9</sup>

In obesity increased abdominal pressure rises caused by fat accumulation especially in the abdominal area. Along with that come the increased gastric basal pressure, the increase transient lower esophagus sphincter relaxation (TLESR), decreased LES tone, and increased risk for developing a hiatal hernia. These conditions will increase the incidence of GERD.<sup>10,22,27</sup>

A study conducted in Canada on 453 patients, found

that overweight and obesity are strong risk factors for the symptoms of GERD and erosive esophagitis. In other studies, an association was found between the higher the BMI level gets and the severity of reflux symptoms and the degree of erosive esophagitis.<sup>28-31</sup>

In this study, the use of drugs which decrease LES tone was significantly associated with the occurrence of erosive esophagitis in cases group, more than control. In a large control case study with samples of 6,215 patients, conducted by Labenz et al, showed that the use of drugs that decrease LES tone not significant to the occurrence of erosive esophagitis.<sup>6</sup> Moki et al concluded hypertension as an independent risk factor for the occurrence of erosive esophagitis. This is possible due to the use of calcium antagonist in treatment of hypertension.<sup>32</sup>

Hongo et al reported a study on the effect of nifedipine on esophageal smooth muscle function. Nifedipine was found to significantly decrease LES tone.<sup>33</sup> Not many other studies had proved the association between these drugs and the occurrence of erosive esophagitis. The drugs had the effect of decrease LES tone, thus increasing gastroesophageal reflux which eventually will cause erosive esophagitis.<sup>22</sup>

As a common flaw in case control design, information about risk factors may be overlooked by the patients or undocumented in the medical records (recall bias). This study was partially retrieving data from the outpatients medical records of Cipto Mangunkusumo hospital and interviews to find risk factors in the patients.

In addition to several limitations that have been mentioned in the discussion, other limitations that should be considered. History of treatment for *Helicobacter pylori* which is also a risk factor for erosive esophagitis, was not examined in this study due to the limit of time. Foods and beverages which also influence the occurrence of erosive esophagitis were also not identified because of difficulties in determining the standard amount and duration of consuming these foods and beverages.

## CONCLUSION

Heavy smoker (>15 cigarettes/day), use of NSAIDs and drugs that decrease LES tone, were the risk factors for the occurrence of erosive esophagitis. Elderly age, male, hiatal hernia, overweight body mass index, and alcoholics cannot be proved as a risk factor for erosive esophagitis.

## SUGGESTION

To be more careful in considering the use of NSAIDs and drugs that decrease LES tone in patients with dyspepsia, as well as to promote anti-smoking.

In studies on risk factors using certain drugs, samples should be better taken from polyclinics which commonly use those drugs, and a cohort design shall serve best. A study on scoring system of risk factors should be conducted, to serve as a tool which may help increase the accuracy in diagnosing erosive esophagitis patients, and there should be a study on a more specific causal relationship between risk factors and the occurrence of erosive esophagitis.

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